REMARKS

Claims 4 and 5 are pending in the instant application. Claims 4 and 5 have been rejected. Claims 4 and 5 have been amended. Reconsideration is respectfully requested in light of the amendments and the following remarks.

I. Rejection of Claim 4 Under 35 U.S.C. 103(a)

Claims 4 and 5 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Zoghbi *et al.* (US Patent Application 2004/0243010). The Examiner suggests that this reference discloses a method of determining the level of BNP in a sample from a patient prior to exercise to establish a baseline, and also determining the level of BNP in a sample from the patient post exercise. The Examiner suggests that the patent teaches that the levels of BNP are determined in pg/ml before and immediately after exercise of the patient and that the increase in the levels after exercise is 13.2 pg/ml, which is greater than 10 pg/ml. The Examiner suggests that this reference also discloses that the exercise stress test can be performed with myocardial perfusion imaging using a dual isotope, rest-stress protocol, and that the lowest detectable measurement of BNP can

be as low as 5 pg/ml. The Examiner acknowledges that the reference fails to disclose determining the absolute level of change in an individual and diagnosing based on that individual, however, the Examiner also suggests that it would have been obvious for one of ordinary skill in the art to determine pre-exercise and post-exercise levels in an individual suspected of suffering ischemic heart disease. The Examiner suggests that one of skill would have had an expectation of success and would be motivated based on common sense and common knowledge. Applicants respectfully disagree with this analysis and conclusions.

Claims 4 and 5 recite a method for detecting cardiac ischemia in an individual suspected of suffering from ischemic cardiovascular disease that comprises measuring actual picrogram per milliliter of blood levels of either BNP or NTproBNP in blood samples from an individual both before and after the individual has completed an exercise stress test with myocardial perfusion imaging wherein a dual isotope, rest-stress protocol is used, and then the active steps of determining an absolute level of change in the actual pg/ml of blood level of BNP or NTproBNP, as well as diagnosing cardiac ischemia by identifying

the absolute level of change in the actual pg/ml of blood level of a peptide as being greater than 10 pg/ml of BNP or as being greater than 5 pg/ml of NTproBNP. Applicants point out that data are provided showing that the method of the present invention is based on measurement of actual picrogram per milliliter of blood levels and that the changes in the blood levels after exercise relate to either the absolute level of change in the actual pg/ml of blood level of a peptide as being greater than 10 pg/ml of BNP or as being greater than 5 pg/ml of NTproBNP.

As previously discussed, and in marked contrast, Zoghbi *et al.* (US2004/0243010) disclose use of an entirely different endpoint for assessing risk of ischemia in patients, including the method involving measurement of blood levels of BNP in the same patient both before and after exercise. As taught in Examples 5-7, and Table 1, pages 9-10 of the application, although BNP increased from baseline to immediately post-exercise in individuals with ischemia as well as those without ischemia, the actual pg/ml change in BNP levels post exercise in patients either with or without ischemia had a median value of 15.5 pg/ml in ischemia patients, *i.e.*, patients diagnosed with ischemia, and that the difference between the change in pg/ml of

BNP between ischemic patients and those identified as being not ischemic was not statistically significant (p-value reported to be 0.115). Therefore, absolute levels of BNP in blood did not differ between such individuals (see paragraphs [0104] and [0105]). As also cited in the earlier response, the language in the patent is also very important as it provides one of skill with the expectation of no success in using absolute levels of BNP or NTproBNP. In fact, the application states ***"Neither the absolute BNP levels at peak nor the absolute level of rise from baseline to immediate post-exercise differentiated between ischemic and non-ischemic patients."*** [see paragraph [0104]). This is an important teaching of Zoghbi *et al.* that speaks to a lack of motivation and also lack of an expectation of success to modify the method of the reference to employ a measure of an absolute change in a blood level of either BNP or NTproBNP in lieu of use of percent change in blood levels of BNP, as is explicitly taught by Zoghbi *et al.* as being the useful measure in populations of patients. This is especially relevant since nowhere does Zoghbi *et al.* teach or suggest the actual magnitude of changes in blood levels of BNP in any individual patients after exercise as compared to before exercise (*i.e.*, individual

patient data are not provided). As a result, not only does Zoghbi et al. fail to provide a motivation to use a different method and endpoint, a method based on absolute changes in blood levels in individuals versus a percent change in a population, as taught by Zoghbi *et al.*, but the application also fails to provide a reasonable expectation of success. This is because, as demonstrated by the data presented by Zoghbi *et al.* in Example 7 (page 10 of the application), there was a wide variability in the baseline levels and post-exercise levels of BNP among subjects, at least a three-fold level of variability (see the ranges of values found at paragraph [0104]). It is this wide range within a population that fails to provide one of skill in the art with an expectation that there would reliably a response in an individual that meets the criteria of the instant invention of absolute changes of only 10 pg/ml for BNP or 5 pg/ml for NTproBNP. The application of Zoghbi *et al.* shows a median increase for the group of greater than 10 pg/ml, which was not different than the median increase in the patient group with ischemia (Example 7). This teaching by Zoghbi et al. is not the same as the methods of claim 4 or newly added claim 5 which recite specifically identifying the actual increases in BNP

(amended claim 4) or NTproBNP blood levels (newly added claim 5), in pg/ml, in a single individual, not a mean value for a group of individuals. In fact, with their teaching, the application of Zoghbi *et al.* teaches away from the method of the present invention which relies on measurement of actual levels of natriuretic peptides in blood, not percent increases as is used by Zoghbi *et al.* It is only mere speculation on the part of the Examiner that one of skill in the art would alter the method of Zoghbi et al., which was developed for use in populations of individuals, such as in a clinical trial for drug development, to use as a diagnostic tool for use in diagnosing disease in individuals when Zohgbi et al. teach explicitly that ***"Neither the absolute BNP levels at peak nor the absolute level of rise from baseline to immediate post-exercise differentiated between ischemic and non-ischemic patients."*** [see paragraph [0104]).

In order to establish a *prima facie* case of obviousness, however, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable

expectation of success. Finally, the prior art must teach or suggest all claim limitations. "In rejecting claims under 35 U.S.C. §103, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993), *citation omitted*. In the instant case, Applicants have shown how Zoghbi *et al*. fail to provide both a motivation and a reasonable expectation of success that could be used to make obvious the invention of amended claim 4. With respect to newly added claim 5, Zoghbi *et al*. also fail to teach and suggest all limitations of the claims since the patent provides absolutely no teaching of monitoring actual levels of NTproBNP where any increase from baseline in such peptide levels is shown to related to any disease, including cardiac ischemia. It is only with the specification in hand that one of skill in the art would have the understanding to use changes in absolute levels of NTproBNP in blood in an individual as a diagnostic tool where the change would exceed 5 pg/ml in that individual. Accordingly, the reference of Zoghbi *et al*. cannot make obvious claims 4 and 5 and withdrawal of this

rejection is respectfully requested. However, in an earnest effort to advance the prosecution and facilitate allowance of the claims, Applicants have amended the claims to recite that the methods of the present invention are "consisting of" the specific cited steps. As already discussed, nowhere does the Zoghbi et al. reference teach the specific steps as cited, and also fails to provide for motivation to modify the method taught in the patent application. Therefore, the claims as amended are not obvious over Zoghbi *et al.* and withdrawal of this rejection is respectfully requested.

II. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Reg. No. 32,257

Date: **April 4, 2011**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053
856-810-1515
Email: jmlicata@licataandtyrrell.com